Gastrointest Interv 2014; 3:40–45

Contents lists available at ScienceDirect

Gastrointestinal Intervention

journal homepage: www.gi-intervention.org

Review Article

Role of endosonography in the management of incidental pancreatic cystic lesions

Yu Man Ching Kelvin,[1] Jin-Seok Park,[2] Dong-Wan Seo[2,*]

A B S T R A C T

The management of incidental pancreatic cystic lesion (PCL) can be challenging. With a better understanding of the natural course of PCL, we recommend surveillance of PCL without high-risk stigmata for at least 5 years. The importance of interventional endoscopic ultrasound (EUS) in establishing a specific diagnosis and treatment cannot be over-emphasized. This review aims to give an overview on the latest developments in EUS-guided fine needle aspiration and EUS-guided pancreatic cyst ablation.

Keywords: Ablation, Endoscopic ultrasound, Pancreatic cyst

Introduction

Incidental pancreatic cysts are diagnosed with increasing frequency because of widespread utilization of cross-sectional imaging. With advances in imaging techniques, asymptomatic (incidental) pancreatic cystic lesions (PCL) can be detected with increased sensitivity. Two consecutive retrospective case series from the same tertiary surgical centers reflect this trend.[1,2] The initial case series reviewed 212 patients who were diagnosed with PCL (mean size = 33 mm) from 1997 to 2002, with 36% of them being incidentally detected. From 2004 to 2007, 401 patients were detected with PCL (mean size = 27 mm), with 71% of them asymptomatic.

Epidemiology and natural course

In the general population, the prevalence of pancreatic cyst is estimated to be 2.6%.[3] In the previous retrospective study, contrast-enhanced multidetector computed tomography (CT) scans of the abdomen were reviewed from 2832 consecutive examinations to identify pancreatic cysts. Patients with a history of pancreatic lesions, with predisposing factors for pancreatic disease, or who were referred for CT of the pancreas were excluded. Mean cyst size on detection was 8.9 mm (range 2–38 mm), and 85% of the cysts were solitary. Cyst occurrence was strongly correlated with increasing age and Asian ethnicity. Approximately 10% of patients older than 80 years were diagnosed with pancreatic cysts, whereas cyst presence was rare in patients younger than 40 years. No gender preponderance was observed.

With increasing data from clinical studies, we have a better understanding of the natural history of PCL. In an earlier retrospective cohort study, 112 patients who had PCL but who were not indicated for surgery were followed-up to assess malignant progression, growth of cysts, need for surgery, and mortality.[4] Exclusion criteria were evidence of pancreatitis or a history of von Hippel–Lindau disease, polycystic disease of the kidney or liver, or cystic fibrosis. During follow-up for the median period of 72.3 months, the size of the PCL increased in 18 patients (16.1%). Six of these patients experienced growth of their PCL after 5 years of follow-up. Twenty-six patients underwent surgery during follow-up, and four malignant cysts were detected. The overall rate of malignant progression during follow-up was 3.6%. The presence of mural nodules or solid components was independently associated with the presence of malignant PCL. The authors concluded that most PCL show favorable prognosis, but long-term surveillance for > 5 years was recommended. In another study, Lee et al investigated natural history of PCL with 182 patients who have incidental PCL. The mean follow-up period was 35.4 months. The results of this study showed that cyst size increased in 54 patients, did not change in 107, and decreased in 21 during follow-up period, and three cases were found to have developed a malignancy. The authors also recommended long-term regular follow-ups of PCL.[5]

A clear understanding of the long-term natural behavior of PCL is essential for investigators to establish a follow-up plan and to

[1] Division of Gastroenterology, Department of Medicine and Geriatrics, Tuen Mun Hospital, Hong Kong
[2] Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea
Received 27 February 2014; Revised 21 April 2014; Accepted 24 April 2014
* Corresponding author. Division of Gastroenterology, Department of Gastroenterology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea.
E-mail address: dwseoamc@amc.seoul.kr (D.-W. Seo).

2213-1795
http://dx.doi.org/10.1016/j.gii.2014.04.003

design clinical guidelines. Thus, accumulation of more long-term data is needed.

Diagnosis and investigations

Documentation of demographic data and detailed history taking are the first important steps for diagnosis. If the patient is male, mucinous cystic neoplasm (MCN) is less likely because it mainly occurs in women. If the patient is young and female, solid pseudopapillary neoplasm should be suspected. MCN tends to occur in middle-aged patients, serous cystadenoma (SCA) can occur in middle-aged to elderly people, and intraductal papillary mucinous neoplasm (IPMN) mostly occurs in the elderly. Pseudocysts are unlikely if there is no history of pancreatitis or trauma. Neuroendocrine tumor and SCA should be considered if there is a history of multiple endocrine neoplasia or von Hippel-Lindau syndrome.

Invasive carcinoma is uncommon in patients with an asymptomatic cyst of 1 cm.[6] Thus, follow-up without further investigation is generally acceptable.

For cysts $>$ 1 cm or for symptomatic cysts, further evaluation with gadolinium-enhanced magnetic resonance imaging (MRI) plus MR cholangiopancreatography or pancreatic protocol multidetector CT is recommended. MRI is the imaging procedure of choice for evaluating a pancreatic cyst due to its better visualization of pancreatic ductal communication (sensitivity 91–100%, specificity 90%), cyst septation, and solid component.[7]

CT and MRI are valuable tools to detect pancreatic cysts. However, the accuracy of MRI and CT to make a specific diagnosis is suboptimal, with reports of 39–50% and 40–44% respectively.[8,9] In predicting benign or malignant disease, CT has a sensitivity and specificity of 36–71% and 64–100%, respectively, whereas MRI has a sensitivity and specificity of 65–77% and 58–89%, respectively.

Studies on 18-fluorodeoxyglucose positron emission tomography (PET) scan studies have produced varying results. Three studies investigated the ability of PET-CT to differentiate between benign and malignant lesions.[10–12] Definitive histology was available in all patients. The reported sensitivity and specificity ranged from 57–94% and 65–97%, respectively. A recent study comparing PET-CT with CT to predict malignancy showed a sensitivity and specificity of 100% and 87% respectively.[13] Further evaluation of PET-CT in multicenter controlled trials is warranted.

Role of endoscopic ultrasonography in diagnosis and risk stratification

Endoscopic ultrasonography (EUS) has become an important tool in the diagnosis and risk stratification of pancreatic cysts. It can accurately visualize the cyst morphology, assess vascular pattern by contrast harmonic scan, and perform fine-needle aspiration (FNA) for evaluation of cytology and molecular markers.

Morphology

Many PCL have typical features. In order to make a presumptive diagnosis by EUS examination, cyst size, number, and shape, state of cyst wall, internal cyst features, presence of calcification or scarring, communication with pancreatic duct, presence of mural nodules, and lymphadenopathy should be carefully inspected (Fig. 1 and 2). However, a number of studies showed low accuracy of EUS alone to determine benign versus malignant disease.[14] In addition, interobserver agreement among endosonographers to morphologically differentiate between mucinous and non-mucinous cysts was shown to be only fair ($\kappa = 0.24$).[15] Thus, EUS alone does not appear to be very reliable to establish a specific diagnosis or to differentiate between benign and malignant disease (Table 1).[16]

EUS-FNA with cyst fluid cytology

Cystic fluid aspirate is acellular or with minimal cellularity in up to 72% of aspirated cysts.[17] Analysis of cystic fluid aspirate can be used to differentiate mucinous from nonmucinous cysts with a sensitivity, specificity, and accuracy of 12.5–27%, 90–100%, and 55%, respectively.[18,19] In another report, cytology was shown to have an accuracy of 50% in differentiating benign from malignant disease.[20] Aspiration may be difficult in SCA because of its microcystic structure. However, the presence of glycogen-rich cells is highly specific to SCA.[21]

Cystic fluid analysis and molecular markers

Carcinoembryonic antigen (CEA) in cyst fluid is one of the most studied tumor markers. It is a useful marker to predict the presence of mucinous cysts but not of malignancy.[21] However, the reported cut-off values vary. In a large prospective study in 2004, the utility of CEA, CA19-9, CA72-4, CA15-3, and CA125 to differentiate mucinous and nonmucinous cysts was evaluated in 341 patients who underwent EUS-FNA of pancreatic cysts.[22] That study suggested that an intracystic CEA level of $\geq$ 192 ng/mL could predict the presence of mucinous cysts with a diagnostic accuracy of 79%, which was superior to either EUS morphology alone (51%) or cytology (59%). However, with this cut-off, about one-fifth of the cases with genuine mucinous cysts would be missed as false negatives. Another study performed a pooled analysis of 12 trials and demonstrated that when CEA levels were $\geq$ 800 ng/mL, the specificity for differentiating mucinous cysts was 98%, whereas the sensitivity dropped to 48%.[23] By contrast, a CEA level $\leq$ 6 ng/mL has been shown to be highly specific for serous/non-mucinous cysts. Hence, we can only conclusively determine the nature of the cysts when the intracystic fluid CEA is $\leq$ 6 ng/mL or $\geq$ 800 ng/mL.

As an enzymatic marker, cyst fluid amylase is useful in the differentiation of pseudocysts from cystic neoplasm. An amylase level $<$ 250 U/L essentially excludes pseudocysts. Another enzymatic marker, serine peptidase inhibitor Kazal type 1 (SPINK1), is a polypeptide synthesized by several types of tumors and cell lines.[24] A previous study evaluated cyst fluid SPINK1 levels in resected pancreatic cystic lesions and found that the levels were significantly higher in main-duct/mixed type IPMN and MCN patients, than in SCN and branch-duct (BD) IPMN patients.[25] Furthermore, SPINK1 may be a predictive marker of the need for surgery in PCL.

Identification of genetic mutations may represent the next frontier for research. The oncogene *GNAS* was recently detected in IPMN tissue as well as in duodenal juice.[26] Some reports have suggested that *GNAS* mutations are prevalent in IPMN, especially in the intestinal form and in invasive IPMN.[27] K-*ras*, *p*16, and *p*53 mutations have also been reported to be associated with progression of pancreatic cysts from nondysplastic to dysplastic cysts.[28]

Treatment strategy

Surgery

Surgery remains the mainstay treatment for pancreatic cystic neoplasms, either to relieve symptoms in nonmucinous benign disease, or to prevent or eliminate malignant neoplasms.

Early resection of premalignant lesions is associated with survival benefit. For example, the prognosis of a resected benign IPMN is excellent with a 10-year survival rate of $>$ 95% or both main-duct

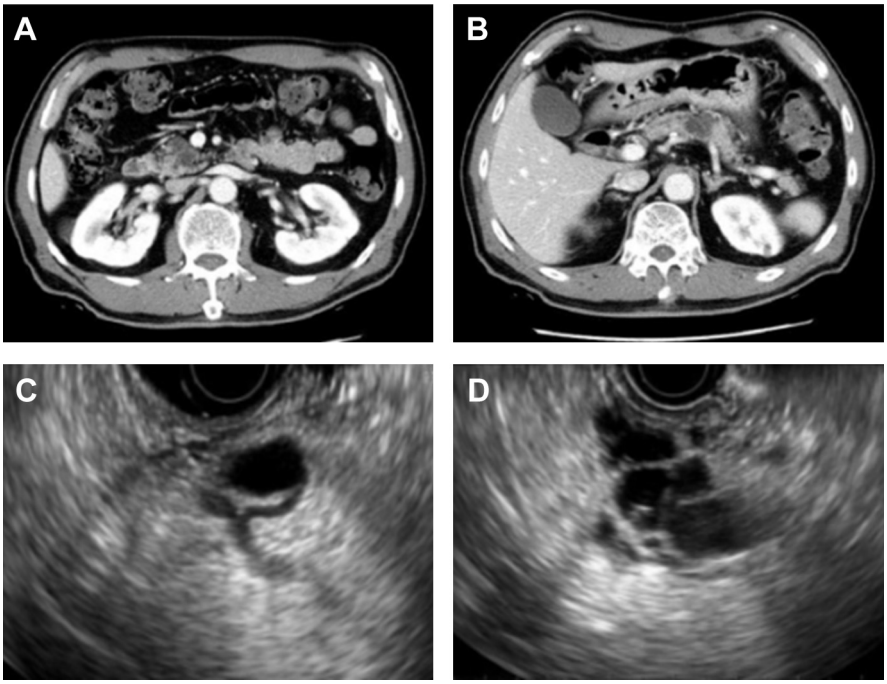

Fig. 1. Branch-duct intraductal papillary mucinous neoplasm. (A, B) computed tomography showing a pancreatic cystic neoplasm at the head of the pancreas and pancreas body respectively. (C) Endoscopic ultrasound at the head of the pancreas showing a 3 cm septated cyst in communication with the pancreatic duct. The main pancreatic duct is mildly dilated, measuring up to 5 mm. (D) Endoscopic ultrasound at the pancreatic body showing a 2.7 cm multiseptated cyst.

and BD tumors.[29] This survival rate drops dramatically to 60% or lower when invasive IPMN-carcinoma is resected.[30]

The 2012 international consensus guidelines outline the management recommendations specifically for IPMN and MCN.[31] "Worrisome features" refer to main pancreatic duct (MPD) dilatation of 5–9 mm, cyst size $>$ 3 cm without "high-risk stigmata", presence of a nonenhanced mural nodule, thickened nonenhanced cyst wall, and abrupt changes in MPD caliber with distal pancreatic atrophy. "High-risk stigmata" describes a cyst with MPD dilatation $>$ 10 mm, or the presence of an enhanced mural nodule.

Surgery is recommended in patients with cystic lesions in association with obstructive jaundice, all surgically fit patients with main-duct-IPMN or MCN, and BD-IPMN patients with high-risk stigmata such as an enhanced solid component. Surgical management of BD-IPMN without high-risk stigmata is subjected to ongoing controversy with regard to the timing and extent of resection, mainly because a highly reliable marker of malignant transformation is lacking. Currently, BD-IPMN without high-risk stigmata is usually monitored closely without immediate surgery.

SCN is rarely associated with malignancy. Surgery is not indicated unless SCN causes mechanical complications due to a large size (usually $>$ 4 cm), or it shows a significant growth tendency of $>$ 2–10 mm/year.[32,33] Solid pseudopapillary neoplasm is associated with some risk of malignancy, whereas malignant transformation of neuroendocrine tumor is difficult to predict. Surgery is best decided in a case-by-case manner.

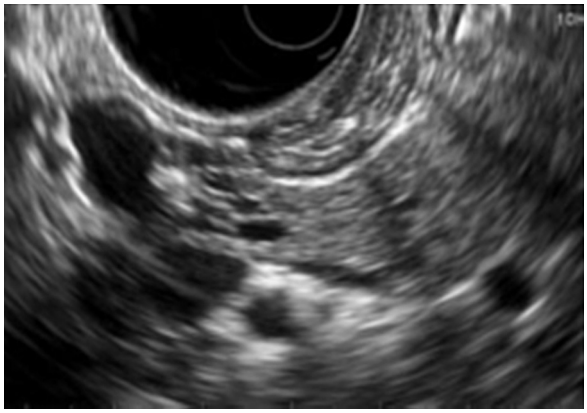

Fig. 2. Serous cystic neoplasm. Endoscopic ultrasound showing typical central stellate calcification and a microcystic component.

Limitation of surgery

Pancreatic resection including pancreatoduodenectomy and pylorus-preserving pancreatoduodenectomy is traditionally a major operation with significant risk. Even in high-volume centers, pancreatectomy is associated with a mortality rate of 0.5–2%, and a morbidity rate of 20–40%. In 20% of cases, the preoperative diagnosis is premalignant or malignant, but the lesion is found to be pathologically benign.

EUS-guided pancreatic cyst ablation

In some cases, achieving patient satisfaction is difficult when discussing options of conservative or surgical management for mucinous PCL without an eminent risk of malignancy. Patients are often not satisfied with either choice: the former involving no treatment of a precancerous disease and the latter being associated with significant complications. Therefore, EUS-guided pancreatic cyst ablation presents an attractive and practical alternative.

EUS-guided ethanol lavage $\pm$ paclitaxel injection

EUS-guided ethanol lavage plus paclitaxel injection is a promising therapeutic modality currently being developed. A pilot study in 2005 showed that ethanol lavage is safe and effective in

Table 1 Summary of Endoscopic Ultrasound Alone in the Diagnosis and Risk Stratification of Pancreatic Cystic Lesions

	Author	No. of patients	Sens. (%)	Spec. (%)	PPV (%)	NPV (%)	Accuracy (%)
Diagnosis	Koito et al 1997[45]	52					92–96
Need for surgery	Frossard et al 2003[46]	127	71	30	49	40	
Determining malignancy	Sedlack et al 2002[19]	34	91	60			82
	Gerke et al 2006[6]	66	48–87	49–80			65–67
	Kim et al 2011[47]	51	96	71.4			
	Lim et al 2013[48]	298	84.2	33.3			

Note. From "Imaging of indeterminate pancreatic cystic lesions: a systematic review," by M.J. Jones, A.S. Buchanan, C.P. Neal, A.R. Dennison, M.S. Metcalfe, and G. Garcea, 2013, *Pancreatology, 13*, pp. 436–42. Copyright 2013, *IAP and EPC*. Adapted with permission.
NPV, negative predictive value; PPV, positive predictive value; Sens, sensitivity; Spec, specificity.

pancreatic cyst ablation.[34] The mechanism involves destruction of cyst epithelium by rapid protein precipitation, cell membrane lysis, and vascular occlusion. Treatment response is further augmented by adding a chemotherapeutic agent, most commonly paclitaxel, which acts by inhibiting the disassembly of microtubules during cell division and subsequently inducing apoptosis.

In selected cases, with a curvilinear echoendoscope, the target cyst can be punctured via the transgastric or transduodenal route with a 22-gauge FNA needle. After aspiration of the cyst fluid, ethanol is injected at a volume equal to that initially aspirated. To be effective, ethanol should be at a concentration of 40% or higher, with 99% ethanol most commonly administered. Ethanol is left for 20–40 minutes followed by evacuation. Paclitaxel can then be injected and left in the cyst cavity. Paclitaxel is prepared as an oil-based viscous form, which minimizes the risk of leaking out of the cyst. Plasma paclitaxel concentrations after EUS-guided pancreatic cyst ablation are almost undetectable and rarely cause systemic side effects. Cross-sectional imaging is usually performed 3–4 months after the injection to evaluate the resolution or change in cyst size (Fig. 3).

Cyst ablation with ethanol plus paclitaxel is usually well tolerated. Abdominal pain is the most common acute complication and is reported in up to 20% of cases within the first week. Other complications include acute pancreatitis (2–4%), intracystic hemorrhage (2%), fever, transient hypotension, alcoholic intoxication, and rarely splenic or portal venous thrombosis. To date, no procedure-related death has been reported.

Another potential disadvantage of this technique is that it commonly induces perilesional fibrosis, which may make future pancreatic surgery more difficult.

Proposed indication

Cyst ablation may be considered for the following conditions[35]: (1) a 2–5 cm benign uni/oligo-loculated MCN or BD-IPMN (without high-risk stigmata) located in the head or body of the pancreas; (2) 2–5 cm benign uni/oligo-loculated MCN or BD-IPMN (without high-risk stigmata) located in the tail of the pancreas in a patient otherwise unfit for surgery (3) MCN or IPMN with high-risk stigmata in a patient who refuses surgery, or who does not tolerate

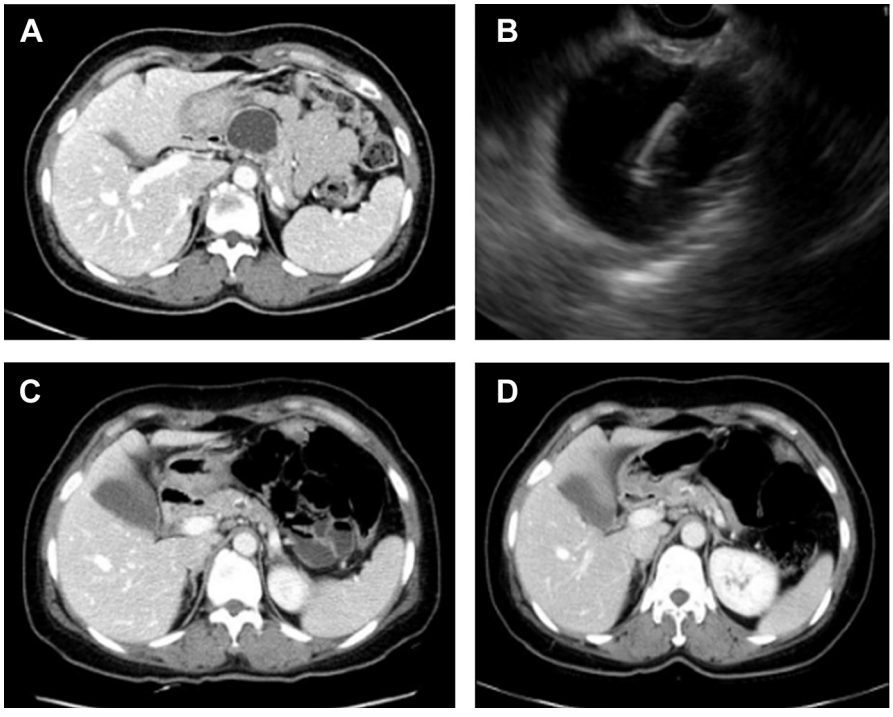

Fig. 3. Complete remission of mucinous cystic neoplasm after endoscopic ultrasound guided ablation. (A) Computed tomography showing a solitary 3.6 cm cystic lesion at the body of the pancreas. (B) Endoscopic ultrasound revealing a uniloculated cyst without communication to the pancreatic duct. Clinically, it is consistent with mucinous cystic neoplasm. Ablation was performed with ethanol lavage followed by paclitaxel injection. (C) Follow-up computed tomography 1 year later showing markedly shrinkage of the cystic lesion (1.2 cm) with peripheral calcification. (D) Follow-up computed tomography 3 years later showing further reduction in the size of the residual cyst, measuring < 1 cm. New lesions are not evident.

Table 2 Summary of Reports on Endoscopic Ultrasound -guided Pancreatic Cyst Ablation

Author	No. of patients	Ablative Agent	Follow-up period, mo	Complete resolution, %	Epithelial denuded in resected cyst, %
Gan et al 2005[34]	25	5–80% ethanol	6–12	35% (8/23)	Variable, up to 100% ($n = 5$)
DeWitt et al 2009[37]	42	80% ethanol	3–4 after 2nd lavage	33% (12/36)	50–100% ($n = 3$)
DiMaio et al 2011[36]	13	80% ethanol	13 after 1st lavage	38% (5/13)	N/A
Oh et al 2008[38]	14	80/99% ethanol + paclitaxel	Median 9 (6–23)	79% (11/14)	N/A
Oh et al 2014[39]	10	99% ethanol + paclitaxel	Median 8.5 (6–18)	60% (6/10)	Partial ($n = 2$)
Oh et al 2011[40]	47	99% ethanol + paclitaxel	Median 20 (12–44)	62% (29/47)	0–100% ($n = 4$)

N/A, not available.

surgery; and (4) macrocystic benign SCN with tendency to develop mechanical complications.

The decision to proceed to cyst ablation relies on a precise diagnosis. In daily practice, around 50% of incidental PCL are classified as indeterminate cysts after thorough initial imaging and EUS ± FNA. The majority of these indeterminate cysts are thought to belong to BD-IPMN or MCN. Nevertheless, further research is needed to address accurate diagnosis, surveillance, and treatment in this group of lesions.

Results and outcomes

From 2005 to 2012, six published prospective studies evaluated the role of EUS-guided pancreatic cyst ablation.[34,36–40] There is heterogeneity among these studies in terms of different ethanol concentrations used, different modalities to define outcome (radiologic vs. EUS), and different design for serial lavage (booster). Three studies used ethanol alone[34,36,37] and three added paclitaxel with ethanol.[38–40] The reports for EUS-guided pancreatic cyst ablation are listed in Table 2.

Cyst resolution or size reduction can be regarded as a surrogate for elimination of cyst epithelium. In the three studies that used ethanol alone for ablation, complete cyst resolution was achieved in 33–40% of patients.[34,36,37] Two of these studies evaluated the histology of surgically resected cysts and showed various degrees (up to 100%) of cyst epithelial denudation.[36,37]

Oh and colleagues[38] reported that the addition of paclitaxel significantly increases CT-defined cyst resolution (size < 5% of the original cyst volume) by 60–79%. The degree of epithelial denudation ranged from 0% to 100% in resected specimens.

Response to cyst ablation can be influenced by cyst characteristics, ablative agents used, and the number of ablations. For cyst factor, a size of the cyst < 3.5 cm was shown to predict complete resolution. Thick cyst wall, multiple septations, and presence of mural nodules are associated with a poor response. Addition of paclitaxel consistently achieved a higher rate of cyst resolution. In addition, treatment with two sessions appears to increase the resolution rate compared with one ethanol ablation.

EUS-guided radiofrequency ablation or photodynamic ablation

Radiofrequency ablation (RFA) is widely used in oncology. This method works by emitting heat energy to induce coagulative necrosis in the target tissue.[41] Recently, there has been growing interest in EUS-guided RFA because pancreatic tissue is very thermosensitive, and EUS has the advantage of real-time visualization and easy access to the pancreas.

Currently, EUS-guided RFA is under investigation for its potential clinical applications. EUS-compatible pilot RFA needles allow for the transduodenal application of RFA. This needle is an 18-gauge endoscopic RFA electrode composed of an electrode covered by protective tubing, an electrode handle, and catheters for the cooling system. The degree of tissue destruction is proportional to the RF energy used, duration of ablation, and length of the RF probe. According to small animal studies, RFA at the pancreatic body and tail appears to be safe with minimal complications, whereas RFA at the pancreatic head is associated with pancreatitis in 20% of cases.[42,43]

EUS-guided photodynamic therapy with the photosensitizing agent porfimer sodium has been shown to be effective in ablation of pancreatic tissue. An animal study demonstrated localized tissue necrosis within the pancreatic tail (range 6.6 – 30.5 mm in diameter). The diameter of the necrotic tissue was directly related to the dose of light. No post-procedural complications were observed.[44]

EUS-RFA or EUS-photodynamic therapy may have some potential but are currently in the preliminary stage of development. The efficacy and safety profile of these techniques require confirmation in large studies with longer follow-up periods. Histological quantification of cyst epithelial or cancer tissue elimination is desirable in future research.

Conclusion

Asymptomatic and incidentally found pancreatic cysts are observed more frequently. Such lesions generally have indolent behavior with a low rate of malignant transformation. Surveillance of selected cases for at least 5 years should be considered. EUS and FNA cytology and molecular marker assessment are important to establish a specific diagnosis and to differentiate benign from premalignant/malignant lesions.

EUS-guided pancreatic cyst ablation with ethanol ± paclitaxel is safe and effective. It is a practical alternative treatment in selected patients who are not candidates for or who refuse surgery.

Conflicts of interest

The authors declare that they have no conflict of interest.

References

1. Fernández-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. *Arch Surg*. 2003;138:427–34.
2. Ferrone CR, Correa-Gallego C, Warshaw AL, Brugge WR, Forcione DG, Thayer SP, et al. Current trends in pancreatic cystic neoplasms. *Arch Surg*. 2009; 144:448–54.
3. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol*. 2008;191:802–7.
4. Ahn DW, Lee SH, Kim J, Yoon WJ, Hwang JH, Jang JY, et al. Long-term outcome of cystic lesions in the pancreas: a retrospective cohort study. *Gut Liver*. 2012;6: 493–500.
5. Lee SH, Shin CM, Park JK, Woo SM, Yoo JW, Ryu JK, et al. Outcomes of cystic lesions in the pancreas after extended follow-up. *Dig Dis Sci*. 2007;52:2653–9.
6. Gerke H, Jaffe TA, Mitchell RM, Byrne MF, Stiffler HL, Branch MS, et al. Endoscopic ultrasound and computer tomography are inaccurate methods of classifying cystic pancreatic lesions. *Dig Liver Dis*. 2006;38:39–44.
7. Berland LL, Silverman SG, Gore RM, Mayo-Smith WW, Megibow AJ, Yee J, et al. Managing incidental findings on abdominal CT: white paper of the ACR incidental findings committee. *J Am Coll Radiol*. 2010;7:754–73.
8. Sainani NI, Saokar A, Deshpande V, Fernández-del Castillo C, Hahn P, Sahani DV. Comparative performance of MDCT and MRI with MR cholangiopancreatography in characterizing small pancreatic cysts. *AJR Am J Roentgenol*. 2009;193: 722–31.

9. Fisher WE, Hodges SE, Yagnik V, Morón FE, Wu MF, Hilsenbeck SG, et al. Accuracy of CT in predicting malignant potential of cystic pancreatic neoplasms. *HPB (Oxford)*. 2008;10:483–90.
10. Frezza AM, Beale T, Bomanji J, Jay A, Kalavrezos N, Dileo P, et al. Is [F-18]-fluorodeoxy-D-glucose positron emission tomography of value in the management of patients with craniofacial bone sarcomas undergoing neo-adjuvant treatment? BMC Cancer. 2014;14:23. http://dx.doi.org/10.1186/1471-2407-14-23.
11. Manohar K, Mittal BR, Kashyap R, Bhattacharya A, Kakkar N, Mete UK. F-18 fluorodeoxy glucose positron emission tomography/computed tomography findings in a rare case of penile leiomyosarcoma. J Clin Imaging Sci. 2011;1:58. http://dx.doi.org/10.4103/2156-7514.90955.
12. Tann M, Sandrasegaran K, Jennings SG, Skandarajah A, McHenry L, Schmidt CM. Positron-emission tomography and computed tomography of cystic pancreatic masses. *Clin Radiol*. 2007;62:745–51.
13. Hong HS, Yun M, Cho A, Choi JY, Kim MJ, Kim KW, et al. The utility of F-18 FDG PET/CT in the evaluation of pancreatic intraductal papillary mucinous neoplasm. *Clin Nucl Med*. 2010;35:776–9.
14. Brugge WR, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, et al. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology*. 2004;126:1330–6.
15. Ahmad NA, Kochman ML, Brensinger C, Brugge WR, Faigel DO, Gress FG, et al. Interobserver agreement among endosonographers for the diagnosis of neoplastic versus non-neoplastic pancreatic cystic lesions. *Gastrointest Endosc*. 2003;58:59–64.
16. Jones MJ, Buchanan AS, Neal CP, Dennison AR, Metcalfe MS, Garcea G. Imaging of indeterminate pancreatic cystic lesions: a systematic review. *Pancreatology*. 2013;13:436–42.
17. Stelow EB, Stanley MW, Bardales RH, Mallery S, Lai R, Linzie BM, et al. Intraductal papillary-mucinous neoplasm of the pancreas. The findings and limitations of cytologic samples obtained by endoscopic ultrasound-guided fine-needle aspiration. *Am J Clin Pathol*. 2003;120:398–404.
18. Attasaranya S, Pais S, LeBlanc J, McHenry L, Sherman S, DeWitt JM. Endoscopic ultrasound-guided fine needle aspiration and cyst fluid analysis for pancreatic cysts. *JOP*. 2007;8:553–63.
19. Sedlack R, Affi A, Vazquez-Sequeiros E, Norton ID, Clain JE, Wiersema MJ. Utility of EUS in the evaluation of cystic pancreatic lesions. *Gastrointest Endosc*. 2002;56:543–7.
20. Wiersema MJ, Vilmann P, Giovannini M, Chang KJ, Wiersema LM. Endosonography-guided fine-needle aspiration biopsy: diagnostic accuracy and complication assessment. *Gastroenterology*. 1997;112:1087–95.
21. Nagula S, Kennedy T, Schattner MA, Brennan MF, Gerdes H, Markowitz AJ, et al. Evaluation of cyst fluid CEA analysis in the diagnosis of mucinous cysts of the pancreas. *J Gastrointest Surg*. 2010;14:1997–2003.
22. Khalid A, Brugge W. ACG practice guidelines for the diagnosis and management of neoplastic pancreatic cysts. *Am J Gastroenterol*. 2007;102:2339–49.
23. Ryu JK, Matthaei H, Dal Molin M, Hong SM, Canto MI, Schulick RD, et al. Elevated microRNA miR-21 levels in pancreatic cyst fluid are predictive of mucinous precursor lesions of ductal adenocarcinoma. *Pancreatology*. 2011;11:343–50.
24. Stenman UH, Koivunen E, Itkonen O. Biology and function of tumor-associated trypsin inhibitor, TATI. *Scand J Clin Lab Invest Suppl*. 1991;207:5–9.
25. Raty S, Sand J, Laukkarinen J, Vasama K, Bassi C, Salvia R, et al. Cyst fluid SPINK1 may help to differentiate benign and potentially malignant cystic pancreatic lesions. *Pancreatology*. 2013;13:530–3.
26. Kanda M, Knight S, Topazian M, Syngal S, Farrell J, Lee J, et al. Mutant GNAS detected in duodenal collections of secretin-stimulated pancreatic juice indicates the presence or emergence of pancreatic cysts. *Gut*. 2013;62:1024–33.
27. Komatsu H, Tanji E, Sakata N, Aoki T, Motoi F, Naitoh T, et al. A GNAS mutation found in pancreatic intraductal papillary mucinous neoplasms induces drastic alterations of gene expression profiles with upregulation of mucin genes. *PLoS One*. 2014;9:e87875.
28. Sugano K. Molecular diagnosis of pancreatic cancer. *Nihon Geka Gakkai Zasshi*. 1997;98:597–603.
29. Fernández-del Castillo C, Adsay NV. Intraductal papillary mucinous neoplasms of the pancreas. *Gastroenterology*. 2010;139:708–13.
30. Wasif N, Bentrem DJ, Farrell JJ, Ko CY, Hines OJ, Reber HA, et al. Invasive intraductal papillary mucinous neoplasm versus sporadic pancreatic adenocarcinoma: a stage-matched comparison of outcomes. *Cancer*. 2010;116:3369–77.
31. Tanaka M, Fernández-del Castillo C, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. *Pancreatology*. 2012;12:183–97.
32. Bassi C, Salvia R, Molinari E, Biasutti C, Falconi M, Pederzoli P. Management of 100 consecutive cases of pancreatic serous cystadenoma: wait for symptoms and see at imaging or *vice versa*? *World J Surg*. 2003;27:319–23.
33. Tseng JF, Warshaw AL, Sahani DV, Lauwers GY, Rattner DW, Fernandez-del Castillo C. Serous cystadenoma of the pancreas: tumor growth rates and recommendations for treatment. *Ann Surg*. 2005;242:413–9.
34. Gan SI, Thompson CC, Lauwers GY, Bounds BC, Brugge WR. Ethanol lavage of pancreatic cystic lesions: initial pilot study. *Gastrointest Endosc*. 2005;61:746–52.
35. Oh HC, Brugge WR. EUS-guided pancreatic cyst ablation: a critical review (with video). *Gastrointest Endosc*. 2013;77:526–33.
36. DiMaio CJ, DeWitt JM, Brugge WR. Ablation of pancreatic cystic lesions: the use of multiple endoscopic ultrasound-guided ethanol lavage sessions. *Pancreas*. 2011;40:664–8.
37. DeWitt J, McGreevy K, Schmidt CM, Brugge WR. EUS-guided ethanol versus saline solution lavage for pancreatic cysts: a randomized, double-blind study. *Gastrointest Endosc*. 2009;70:710–23.
38. Oh HC, Seo DW, Lee TY, Kim JY, Lee SS, Lee SK, et al. New treatment for cystic tumors of the pancreas: EUS-guided ethanol lavage with paclitaxel injection. *Gastrointest Endosc*. 2008;67:636–42.
39. Oh HC, Seo DW, Kim SH, Min B, Kim J. Systemic effect of endoscopic ultrasonography-guided pancreatic cyst ablation with ethanol and paclitaxel. Dig Dis Sci; 2014;. http://dx.doi.org/10.1007/s10620-014-3037-2. [Epub ahead of print]
40. Oh HC, Seo DW, Song TJ, Moon SH, Park do H, Soo Lee S, et al. Endoscopic ultrasonography-guided ethanol lavage with paclitaxel injection treats patients with pancreatic cysts. *Gastroenterology*. 2011;140:172–9.
41. Carrara S, Arcidiacono PG, Albarello L, Addis A, Enderle MD, Boemo C, et al. Endoscopic ultrasound-guided application of a new hybrid cryotherm probe in porcine pancreas: a preliminary study. *Endoscopy*. 2008;40:321–6.
42. Gaidhane M, Smith I, Ellen K, Gatesman J, Habib N, Foley P, et al. Endoscopic ultrasound-guided radiofrequency ablation (EUS-RFA) of the pancreas in a porcine model. *Gastroenterol Res Pract*. 2012;2012:431451.
43. Kim HJ, Seo DW, Hassanuddin A, Kim SH, Chae HJ, Jang JW, et al. EUS-guided radiofrequency ablation of the porcine pancreas. *Gastrointest Endosc*. 2012;76:1039–43.
44. Yusuf TE, Matthes K, Brugge WR. EUS-guided photodynamic therapy with verteporfin for ablation of normal pancreatic tissue: a pilot study in a porcine model (with video). *Gastrointest Endosc*. 2008;67:957–61.
45. Koito K, Namieno T, Nagakawa T, Shyonai T, Hirokawa N, Morita K. Solitary cystic tumor of the pancreas: EUS-pathologic correlation. *Gastrointest Endosc*. 1997;45:268–76.
46. Frossard JL, Amouyal P, Amouyal G, Palazzo L, Amaris J, Soldan M, et al. Performance of endosonography-guided fine needle aspiration and biopsy in the diagnosis of pancreatic cystic lesions. *Am J Gastroenterol*. 2003;98:1516–24.
47. Kim JH, Eun HW, Park HJ, Hong SS, Kim YJ. Diagnostic performance of MRI and EUS in the differentiation of benign from malignant pancreatic cyst and cyst communication with the main duct. *Eur J Radiol*. 2012;81:2927–35.
48. Lim LG, Lakhtakia S, Ang TL, Vu CK, Dy F, Chong VH, et al. Factors determining diagnostic yield of endoscopic ultrasound guided fine-needle aspiration for pancreatic cystic lesions: a multicentre Asian study. *Dig Dis Sci*. 2013;58:1751–7.